ANRS 0392s ELDORADO - Information for researchers

Title :

PHASE III, OPEN-LABEL, RANDOMIZED, MULTICENTER TRIAL EVALUATING THE NON-INFERIORITY OF DORAVIRINE VERSUS DOLUTEGRAVIR BASED ANTIRETROVIRAL REGIMENS IN TREATMENT-NAÏVE PEOPLE LIVING WITH HIV-1 INFECTION

Short title: ANRS0392s
ELDORADO

EU-CT number: 2023-508626-10-00
ClinicalTrials.gov number: NCT06203132

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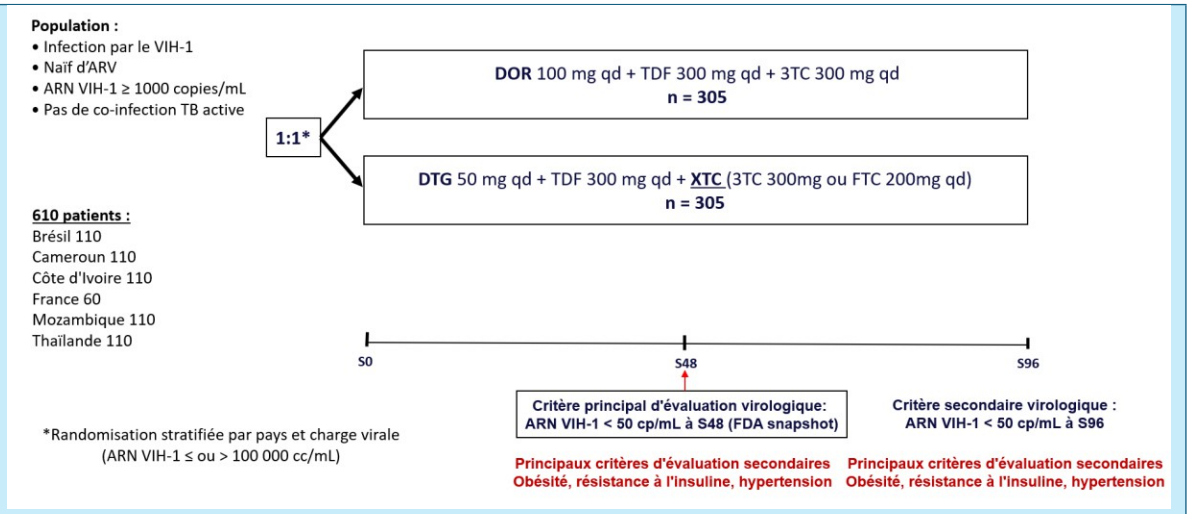
	Date of first inclusion: 10/02/2025 Research end date: Second quarter 2028
	Number of participants expected/recruited: 610/21
	Participating countries and number of sites : - France (N=9) - Ivory Coast (N=3) - Mozambique (N=1) - Thailand (N=3) - Brazil (N=2) - Cameroon (N=1)
	Research status: In progress
	Pathology: HIV-1
	Promotion: Inserm-ANRS MIE Co-funded by : ANRS MIE, MSD and EDCTP3. - **EDCTP3:** Global Health EDCTP3 (European and Developing Countries Clinical Trials Partnership 3) is a partnership between the European Union, represented by the European Commission, and the EDCTP Association, representing the governments of 15 European countries and 30 sub-Saharan African countries. (https://www.global-health-edctp3.europa.eu/index_en)
	Funded under: AAP 2023-1
The project	The ANRS0392s ELDORADO trial is a Phase III, open-label, randomized, multicenter trial designed to assess the non-inferiority of **DORAvirine** versus **DOlutegravir** in antiretroviral treatment-naive people living with HIV-1. Antiretroviral therapy (ART) blocks the multiplication of HIV in the blood (measured by HIV viral load), thereby improving immune defenses (measured by CD4 cell count). Under treatment, people with HIV are less susceptible to HIV complications. Since 2018, the reference ART recommended by the WHO for treatment-naive people living with HIV-1 is dolutegravir. While this treatment has proven its efficacy, recent studies have reported metabolic disorders associated with its use (weight gain, hypertension and diabetes). Doravirine is a new drug that appears to be very well tolerated. It is recommended as an alternative treatment by the International Antiviral Society-USA (IAS-USA), and is indicated as first-line treatment by the European AIDS Clinical Society (EACS). In many parts of the w o r l d , it i s therefore one of the first-line treatments offered to patients. diagnosed with HIV-1. Although doravirine has already been compared to many

	antiretroviral treatments with good efficacy, it has not yet been compared with dolutegravir in antiretroviral treatment-naive individuals. The aim of this research is to show that doravirine-based ART is non-inferior in efficacy to dolutegravir-based ART. The advantage of this combination would be to reduce the side effects associated with dolutegravir, notably the moderate weight gain observed in patients receiving dolutegravir. If the results of this research are conclusive, doravirine-based treatment could be extended and recommended for ART-naive HIV-1-infected individuals. The primary objective is to determine whether participants on doravirine have a non-inferior response to their treatment compared with participants on dolutegravir. This non-inferiority will be determined after 48 weeks of treatment by comparing HIV-1 viral load in the blood according to the treatment received. Secondary objectives of the research included comparison of HIV-1 levels in the blood between the two treatments after 96 weeks of treatment (22 months), assessment of treatment resistance in the event of failure, and side effects (including obesity, hypertension or diabetes). **Test strategies :** At week 0, participants will be randomized in a 1:1 ratio to start ART immediately and receive it until week 96 : • Doravirine arm: DOR+TDF+3TC (doravirine+ tenofovir+ lamivudine) • Dolutegravir arm: DTG+TDF+XTC (dolutegravir+ tenofovir+ lamivudine or emtricitabine) **Research schedule :** • First inclusion: February 10, 2025. • Inclusion period: 18-24 months. • Duration of follow-up for each participant: 96 weeks. • Last visit for the last participant: Second half of 2028. • Total trial period: 4 years. **Metabolic substudy** The trial will include a substudy of changes in fat distribution, markers of adipose tissue and immune activation, and fat quality. This sub-study will include 80 women in the trial, including 40 women treated with doravirine+TDF+3TC, 40 women treated with DTG+TDF+XTC. In France, a total of 10 women will be included in this sub-study. **Trial design**

	
Latest news	The ANRS0392s ELDORADO trial began in France in the first quarter of 2025. The first trial participant was recruited in France on February 10, 2025, and recruitment for the trial is due to start soon in Brazil. The project has been accepted for co-financing by EDCTP3 in sub-Saharan African sites. The other sites in other countries (Côte d'Ivoire, Mozambique, Cameroon and Thailand) will be activated from July to November 2025, once the EDCTP3 project has officially got underway and all the conditions have been met for inclusion in the countries concerned. The official launch of the EDCTP3 project is scheduled for May 2025.
References Publications	NA
Type study	Phase III, open-label, randomized, multicenter drug trial
Main objectives	To assess the non-inferiority of doravirine in combination with tenofovir and lamivudine, versus dolutegravir in combination with tenofovir and lamivudine or emtricitabine, in terms of virological efficacy at week 48, measured by the proportion of subjects achieving HIV-1 RNA < 50 copies/mL, in treatment-naive HIV-1-infected subjects with a pre-therapeutic viral load (HIV-1 RNA) ≥ 1,000 copies/mL
Secondary objectives	• **Key safety objectives :** Compare the safety of the two treatment schemes in terms of : 1. Presence of obesity at week 48 and week 96 2. Presence of insulin resistance at week 48 and week 96 3. Presence of hypertension at week 48 and week 96 • **Virological objectives :** 4. To assess the non-inferiority of doravirine in combination with tenofovir and lamivudine versus dolutegravir in combination with tenofovir and lamivudine or emtricitabine, in terms of virological efficacy at week 96. Compare the virological efficacy of the two treatment regimens in terms of : 5. Virological failures 6. Presence of HIV-1 drug resistance in patients with confirmed virological failure

	7. Virological efficacy at a threshold of HIV-1 RNA<200 copies/mL at week 48 and week 96 8. Virological efficacy at a threshold of HIV-1 RNA<1000 copies/mL at week 48 and week 96 9. Changes in RT and integrase mutations at inclusion on virological response to week 48 and week 96 • **Other safety targets :** Compare the safety of the two treatment schemes in terms of : 10. Presence of overweight or obesity at week 48 and week 96 11. Presence of weight gain at week 48 and week 96 12. Change in absolute weight gain at week 48 and week 96 13. Presence of diabetes at week 48 and week 96 14. Safety and tolerability of doravirine versus dolutegravir at week 48 and week 96 15. Impact on quality of life at week 48 and week 96 16. Variation in waist circumference, hip circumference and waist-hip ratio at week 48 and week 96 17. Changes in fasting blood glucose and insulin at week 48 and week 96 18. Changes in fasting serum lipids at week 48 and week 96 19. Change in creatinine clearance at week 48 and week 96 20. Presence of acquired immunodeficiency syndrome (AIDS), immune reconstitution inflammatory syndrome (IRIS) or death at week 48 and week 96. • **Other objectives :** Compare the two treatment schemes in terms of : 21. Change in CD4 cell count, CD4 percentage, CD8 cell count, CD8 percentage, CD4/CD8 ratio, week 48 and week 96 22. Antiretroviral treatment compliance at week 48 and week 96 23. Description of the distribution of CYP3A5 mutations in relation to ART and their impact on virological response. 24. Exploration of additional polymorphisms (UGT1A1, ABCB1) based on the state of the art literature. • **Objectives of the metabolic substudy :** 25.a Variation in abdominal fat distribution at week 48 and week 96 25.b Variation in adipose tissue and immune activation markers at week 48 and week 96 25.c Variation in fat quality at week 48
Link to the research website	https://register.clinicaltrials.gov/prs/beta/studies/S000DX7400000218/recordSummary https://anrs.fr/fr/recherche/projets-de-recherche/projet-eldorado/

Criteria inclusion	• Be at least 18 years of age on the day you sign the informed consent form. • Be HIV-1 positive, in line with national testing strategies. • Plasma HIV-1 RNA ≥1000 copies/mL within 30 days of randomization. • Have an indication for HIV treatment based on assessment by a physician in accordance with local treatment guidelines. • Naïve to antiretroviral therapy for the treatment of HIV-1 infection, including experimental antiretroviral agents. Note: Naïve is defined as having received no antiretroviral therapy (0 days) for the treatment of HIV infection. Subjects who have received oral pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) are eligible to participate in this trial, if treatment was terminated more than three months prior to HIV-1 diagnosis and a negative HIV-1 test was performed more than three months prior to HIV diagnosis. • For transgender women or men of childbearing potential, i.e. of childbearing age but not menopausal, or permanently infertile (e.g. tubal obstruction, hysterectomy, bilateral salpingectomy) or not abstaining from sexual activity: negative urine pregnancy test and willingness to use contraceptive methods. • Understand the study procedures and voluntarily agree to participate by giving your written informed consent for the trial. • For participants in France, to be affiliated to the Social Security, to the CMU (Couverture Maladie Universelle) or AME (Aide Médicale d'Etat). Note: Patients with chronic hepatitis B (and/or C) may participate in the study provided they meet all inclusion criteria, have stable liver function tests and no significant impairment of liver synthesis function (significant impairment of liver synthesis function is defined as serum albumin <2.8 mg/dL or INR >1.7 in the absence of any other explanation for the abnormal laboratory test value).
Inclusion criteria: any of the following of the following	• Active tuberculosis (pulmonary or extra-pulmonary) • To any past or present evidence of a disease, therapy, laboratory abnormality or other circumstance likely to distort the results of the study or interfere with the patient's participation for the duration of the study, such that it is not in the patient's best interest to participate in the study. • Is infected with HIV-2 or co-infected with HIV-1 and HIV-2 • Received pre-exposure prophylaxis (PrEP) with long-acting cabotegravir or dapivirine. • Has received oral pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) within the last three months or has not had negative HIV-1 serology. • Has documented or known resistance, or possible resistance to study drugs (in France and in countries where national guidelines recommend screening for primary resistance before starting first-line ART), as defined by the ANRS-MIE AC43 Resistance Group. • Presents the following laboratory values at screening visit within 30 days prior to randomization: - AST (SGOT) and ALT (SGPT) >4.0x upper limit of normal - Estimated glomerular filtration rate at time of screening <60 mL/min/1.73m², based on the CKD-EPI equation

	• Has participated in a study involving an investigational compound/device within the 30 days prior to signing the informed consent or plans to participate in such a study involving an investigational compound/device during the course of this study. • Have used systemic immunosuppressive therapy or immune modulators within 30 days prior to treatment in this study, or are likely to require them during the study. • Requires or is likely to require any of the prohibited or contraindicated drugs mentioned in the trial protocol. • Significant hypersensitivity or other contraindication to any component of the study drugs. • Is pregnant, breastfeeding or planning to conceive at any time during the study. • - Presents any condition that, in the opinion of the investigator, could compromise the safety of the treatment and/or the patient's compliance with study proceduresIs a person under guardianship or deprived of liberty by judicial or administrative decision.
Primary endpoints	• Proportion of subjects virologically successful, defined as achieving HIV-1 RNA <50 copies/mL at week 48 on the treatment assigned at randomization using the FDA "snapshot" algorithm (week 42 to 54 window).
Secondary endpoints	**Key safety evaluation criteria :** 1. Presence of obesity at week 48 and week 96 2. Proportion of subjects with newly measured HOMA ≥2 at week 48 and week 96 vs. inclusion. 3. Proportion of subjects with newly detected hypertension at week 48 and at week 96 compared with inclusion. **Virological evaluation criteria :** 4. Proportion of subjects virologically successful, defined as achieving HIV-1 RNA <50 copies/mL at week 96 on the treatment assigned at randomization, using the FDA snapshot algorithm with a window from week 90 to 102. 5. Proportion of confirmed virological failures occurring up to week 48 and up to week 96. 6. Frequency of HIV-1 drug resistance in patients with confirmed virological failure. 7. Proportion of subjects achieving HIV-1 RNA <200 copies/mL on treatment assigned at randomization at week 48 and week 96. 8. Proportion of subjects achieving HIV-1 RNA <1000 copies/mL on treatment assigned at randomization at week 48 and week 96. 9. Frequency of RT and integrase mutations at inclusion and impact on response virological results at week 48 and week 96 **Other safety evaluation criteria :** 10. Presence of overweight or obesity at week 48 and week 96 11. Proportion of subjects with absolute weight gain ≥10% from baseline at week 48 and week 96. 12. Change from baseline in absolute weight at week 48 and week 96 13. Proportion of subjects with newly diagnosed diabetes at week 48 and week 96 compared with inclusion 14. Any adverse event, regardless of grade, at week 48 and week 96 15. Change from baseline in EQ-5D-3L score at week 48 and week 96

	16. Change from baseline in waist and hip circumferences and waist-to-hip ratio at week 48 and week 96 17. Change from baseline in fasting plasma glucose and insulin at weeks 48 and to week 96 18. Change from baseline in fasting serum lipids at week 48 and at week 96 19. Change from baseline in creatinine clearance at week 48 and week 30 week 96 20. Proportion of subjects with AIDS, defined as CDC stage 3 or WHO stage 4 and tuberculosis, an IRIS or died at week 48 and week 96. **Other evaluation criteria :** 21. Change from baseline in CD4 count (cells/mm3), CD4 percentage, CD8 count (cells/mm3), CD8 percentage, CD4/CD8 ratio, at week 48 and week 96 22. Adherence to ART measured by 1) tablet count (assuming a rate of tablet count compliance <95% as suboptimal compliance), 2) questions on compliance over the last 4 days and past month at each trial visit, and 3) by quantification of TFV-DP in Dried Blood Spots (LC/MS) at week 48 and week 96. 23. Type and frequency of allelic variants in the gene encoding CYP3A5 and impact on DOR and DTG pharmacokinetics, virological response and side effects 24. Assess additional UGT1A1 and ABCB1 polymorphism at inclusion. **Metabolic substudy evaluation criteria** 25.a Change from inclusion in abdominal fat distribution at week 48 and week 96 25.b Change from baseline in adipose tissue markers (adinopectin, leptin) and immune activation markers (sCD14, sCD163) at week 48 and week 96 25.c Change from inclusion (by abdominal subcutaneous surgical biopsy) in adipose tissue pathology, gene expression and global analysis of the transcriptome (RT-PCR and RNAseq) at week 48.

Contents

A - Study methodology and type of data and/or samples collected

Data and samples collected	**Biotech libraries**	-Plasma at every visit from S0 onwards -Whole blood at S0 -DBS at each visit from S4 Substudy only -Serum at S0, S48 and S96 -Subcutaneous biopsies at S0 and S48
	Data	Clinical, biological, imaging, pharmacological, quality of life

Schedule of trial participants

	SCR1	S0	S4	S12	S24	S36	S48	S72	S96	Visit VF[10]
Viewing window	*30 days before S0*		*+/- 4 days*	*+/- 4 days*	*+/- 4 days*	*+/- 7 days*	*+/- 7 days*	*+/- 7 days*	*+/- 7 days*	*In the 2 to 4 weeks depending on VF*
Information	X									
Informed consent	X									
Randomization		X								
Age, height	X									
Medical history including use of PrEP or PEP	X									
Clinical evaluation	X	X	X	X	X	X	X	X	X	X
Collection of adverse events			X	X	X	X	X	X	X	X
Weight and body mass index (BMI)	X	X	X	X	X	X	X	X	X	
Waist and hip circumference		X			X		X		X	
Blood pressure and temperature		X	X	X	X	X	X	X	X	
Chest X-ray	X									
Quality of life questionnaire (EQ-5D-3L)		X					X		X	
Dispensing ART		X	X	X	X	X	X	X		
ART adherence (pill count and adherence over last 4 days/months)			X	X	X	X	X	X	X	X
Local laboratory tests										
Documented discriminatory HIV test	X									
Genotypic resistance testing	X									X[2]
Plasma HIV-1 RNA	X		X	X	X	X	X	X	X	X
CD4 and CD8 counts and percentages, CD4/CD8 ratio	X						X		X	
Blood cell count (CBC)	X	X	X	X	X		X		X	
Transaminases (ASAT, ALAT)	X	X	X	X	X		X		X	
Creatinine	X	X	X	X	X		X		X	
Fasting serum lipids (total cholesterol, HDL, LDL, triglycerides)[4]		X			X		X		X	
Fasting blood glucose[4]		X			X		X		X	
HbA1C[5]		X			X		X		X	
Urine pregnancy test[3]	X	X	X	X	X	X	X	X	X	

Protein and urine glucose		X					X		X	
Biobank samples										
DBS (Dried blood spot)[6,8]			X	X	X	X	X	X	X	X
Frozen samples: Whole blood, plasma[7]		X	X[11]	X	X[11]	X	X	X	X	X
Metabolic substudy										
Adipose tissue biopsy[8,9]		X					X			
Scan DEXA[8,9]		X					X		X	
Adiponectin, leptin, sCD14, sCD1638[9]		X					X		X	
Blood volume										
Maximum number of blood tubes collected (*+ sub-study*)	6	11 *(+1)*	4	4	7	2	9 *(+1)*	2	9 *(+1)*	4
Maximum volume (mL) of blood drawn (*+ substudy*)	30	55 *(+5)*	20	20	35	10	45 *(+5)*	10	45 *(+5)*	20

[1]Screening within 30 days before S0
[2]Genotypic resistance test to be performed in the event of virological failure
[3]For all transgender women and men who are able to have children
[4]To be taken after a strict 12-hour fasting period.
[5]Only for patients with diabetes mellitus
[6]Quantification of TFV-DP (compliance measurement)
[7]For insulin assays, HOMA, virological, pharmacokinetic and pharmacogenomic analyses.
[8]Centralized analysis
[9]Only for metabolic substudy
[10]Virological failure test (VF) to be performed within 2 to 4 weeks of obtaining an HIV-1 RNA≥200 copies/ml.
[11]S4 and S24: Patient must be sampled before taking daily medication.

Sampling circuit : Biothèque

Various types of blood sampling are planned throughout the trial, at each visit from S0 onwards (randomization visit); they are detailed in the table below. As part of the metabolic sub-study, abdominal subcutaneous biopsies are also planned at S0 and S48, to be either frozen or embedded in kerosene.
Once collected, the samples will be temporarily stored in the laboratories of the study sites before being transferred to the ANRS CRB for centralization. Samples will then be sent to the various partner laboratories for centralized analysis.

Visit	SCR	S0	S4	S12	S24	S36	S48	S72	S96	VF1
For all participants										
Dried Blood Spot			X	X	X	X	X	X	X	X
Plasma - Test for genotypic resistance		X								X
Plasma - Insulin dosage		X					X		X	
Plasma - HIV-1 RNA Pharmacokinetics		X	X[2]	X	X[2]	X	X	X	X	X
Whole blood - Pharmacogenomics		X								
Maximum number of tubes for centralized analyses		4	1	1	1	1	2	1	2	2
Maximum volume (mL) sampled for analysis centralized		20	5	5	5	5	10	5	10	10
For participants in the metabolic substudy										
Serum - Metabolic markers (adiponectin, leptin sCD14 and sCD163) [3]		*X*					*X*		*X*	
Total volume (mL) *(+ sub-study)*		20 *(+5)*	5	5	5	5	10 *(+5)*	5	10 *(+5)*	10

1 The virological failure visit should be performed within 2 to 4 weeks after an HIV-1 RNA≥200 copies/mL.
2 The sample must be taken before the daily intake of the drug for pharmacokinetic purposes.
3 If the patient has agreed to participate in the metabolic sub-study only.

B - How to access the collection

1- project submission**: via the website's sample request form**

2- project evaluation: **scientific committee or independent experts**

3- Making the collection available**: final decision by ANRS MIE management or Scientific Advisory Board**

Contact e-mail address for submitting your project : **biobanque@anrs.fr**